(d) clone 78-8-3-E6-CL0_1 of ATCC deposit number 98922.

45. A solid support having a nucleotide sequence affixed thereto, wherein said nucleotide sequence comprises a sequence encoding a full length polypeptide encoded by a human cDNA of a clone selected from any one of:

(a) clone 47-14-1-C3-CL0_5 of ATCC deposit number 98921;

(b) clone 51-11-3-D5-CL1_3 of ATCC deposit number 98922;

(c) clone 51-15-4-A12-CL11_3 of ATCC deposit number 98921; or

(d) clone 78-8-3-E6-CL0_1 of ATCC deposit number 98922.

IN THE FIGURES:

Please replace Figure 9 with the amended version of Figure 9 provided with the accompanying Request for Approval of Drawing Changes.

REMARKS

Claim Amendments

Applicants have added new claims which recite the nucleic acids of SEQ ID NOs: 66, 76, 78 and 124 solely for the purpose of expediting prosecution of the present application. Accordingly, Applicants preserve full rights to prosecute claims relating to the nucleic acids of SEQ ID NOs: 71, 113, 117, 118 and 123 in continuing applications without limitation.

Objections to the Specification

Figure 9 has been amended as indicated in the accompanying red-lined version of the figure in order to include the SEQ ID NOs. of the sequences in which the listed motifs are found and their locations within these SEQ ID NOs.

Rejections of Claims 3, 4, 5, 7 and 8 Under 35 U.S.C. § 112

The Examiner rejected Claims 3, 4, 5, 7 and 8 under 35 U.S.C. § 112, first paragraph on the assertion that they contained subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner

asserted that the specification did not indicate the identities of the full length polypeptides, mature polypeptides, or signal peptides.

Claims 3, 4, 5, 7 and 8 have been cancelled. However, as some of the new claims recite the mature polypeptides or the full length polypeptides, Applicants note that the specification contains two tables, namely Table IV (page 166-172) and Table V (pages 173-178), which describe the locations of full coding sequences, signal peptides and mature polypeptides on each polynucleotide (Table IV) and each polypeptide (Table V) of the invention. In addition, the locations of full coding sequences, signal peptides and mature polypeptides are described as features for each polynucleotide and each polypeptide of the invention in the Sequence Listing. Therefore, Applicants maintain that the claimed sequences are well defined and disclosed in the application in a way that a person skilled in the art would recognize that Applicants were in possession of the claimed invention at the time of filing. Thus, Applicants submit that the requirement of the first paragraph of 35 U.S.C. § 112 have been satisfied and respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Applicants note that some of the new claims recite the positions of the full length, mature and signal polypeptides within the disclosed nucleic acid or polypeptide sequences. As discussed above, Applicants maintain that the recited positions are supported in Tables IV and V as well as in the Sequence Listing.

With respect to the Examiner's concerns that the polypeptides may undergo multiple rounds of processing, the Examiner has not provided any evidence that the claimed polypeptides undergo multiple processing. Furthermore, as discussed above, Applicants have provided the location of the cleavage site at which processing takes place to generate the mature polypeptide.

Rejection of Claims 1-8, 13, 14, 16, 18 and 19 under 35 U.S.C. § 101

The Examiner rejected Claims 1-8, 13, 14, 16, 18 and 19 under 35 U.S.C. § 101 on the assertion that they lack either a specific and substantial utility or a well-established utility. As discussed above, Applicants have amended the claims to recite the nucleic acids of SEQ ID NOs: 66, 76, 78 and 124, solely to expedite the prosecution of the present application. Applicants maintain that the specification meets all the requirements of 35 U.S.C. § 101 with respect to the claimed nucleic acids.

In contrast to the Examiner's assertion, the specification provides a specific utility for the claimed nucleic acids. The biological activities of the polypeptides encoded by the claimed nucleic acids is set forth in the specification in Example 64 (from page 134, line 27, to page 147, line 14).

In particular, the specification identifies the polypeptide of SEQ ID NO: 167, encoded by the polynucleotide of SEQ ID NO: 66 (internal designation 47-14-1-C3-CL0 5), as a homologue of members of the aspartyl protease family that may be involved in protein degradation. (See specification page 146, lines 7-16). In fact, as indicated in the results of the BLASTP analysis provided herewith as Exhibit A, the polypeptide of SEQ ID NO: 167 is 99% identical over most of its length (321 amino acids out of 351 amino acids) to the human beta-secretase precursor (BACE). As described in the publications attached herewith as Exhibits B-F (Yan et al., Nature (1999); 402:533-7; Hussain et al., Mol. Cell. Neurosci. (1999) 14:419-27; Sinha et al., Nature (1999) 402:537-40; Vassar et al., Science (1999) 286-735-41; Lin et al., Proc. Natl. Acad. Sci. USA (2000) 97:4156-60), the BACE protein is an aspartic protease partly responsible for the proteolytic processing of the amyloid precursor protein (APP) into the amyloid beta-peptide which is the major component of the amyloid plaques found in Alzheimer's disease patients and is thought to be causal for the pathology. The specification provides numerous methods for using the claimed nucleic acids in diagnostic and therapeutic methods. These include the methods set forth in Examples 25, 26, 53, 59-61, as well as other methods described elsewhere in the specification.

The specification also identifies the polypeptide of SEQ ID NO: 177, encoded by the polynucleotide of SEQ ID NO: 76 (internal designation 51-11-3-D5-CL1 3), as a homologue of serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz). (See specification page 140, line 24, to page 141, line 6). In fact, as indicated in the results of the BLASTP analysis provided herewith as Exhibit G, the polypeptide of SEQ ID NO: 177 contains a Kunitz domain, including the inhibitory site, similar to the one observed in serine protease inhibitor proteins. The polypeptide of SEQ ID NO: 177 is thus a serine protease inhibitor of the Kunitz family. Kunitz type protease inhibitors are useful in treating several pathologies. For example, as described in Exhibit H (Abraham, Crit. Care Med (2000); 28(19 Suppl):S31-3), the

Kunitz type Tissue Factor Pathway inhibitor has proven to be useful in improving, and even preventing, the outcome of severe sepsis associated with multiple organ failure. The specification provides numerous methods for using the claimed nucleic acids in diagnostic and therapeutic methods. These include the methods set forth in Examples 25, 26, 53, 59-61, as well as other methods described elsewhere in the specification.

In addition, the polypeptide of SEQ ID NO: 177 or part thereof may be used in a "cocktail" with other protease inhibitors to prevent degradation of protein samples. The advantage of using a cocktail of protease inhibitors is that one is able to inhibit a wide range of proteases without knowing the specificity of each of the protease inhibitors. Using a cocktail of protease inhibitors also protects a protein sample from a wide range of future unknown proteases which may contaminate a protein sample from a vast number of sources. Such protease inhibitor cocktails (see for example the ready to use cocktails sold by Sigma) are widely used in research laboratory assays to prevent protein degradation. Thus, those of skill in the art recognize that protease inhibitors may be used in cocktails to prevent protein degradation.

The specification also identifies the polypeptide of SEQ ID NO: 179 encoded by the polynucleotide of SEQ ID NO: 78 (internal designation 51-15-4-A12-CL11_3) as a homologue of mammalian colipase precursors that may play a role in lipid metabolism. (See specification page 146, line 18, to page 147, line 2). Colipases are secreted cofactors for pancreatic lipases that play a crucial role in the intestinal digestion and absorption of dietary fats. In fact, as indicated in the results of the BLASTP analysis provided herewith as Exhibit I, the polypeptide of SEQ ID NO: 179 displays homology to a human colipase domain including the conserved cysteines residues characteristic of this protein family. Thus, inhibition of the expression of the polynucleotide of SEQ ID NO: 78, using methods including those described in Examples 59-61 of the specification, may be used to reduce the absorption of dietary fats in overweight people and in treating disorders such as obesity or diabetes.

The specification also identifies the polypeptide of SEQ ID NO: 225, encoded by the polynucleotide of SEQ ID NO: 124 (internal designation 78-8-3-E6-CL0_1), as a member of the phosphatidylethanolamine-binding protein family (see specification page 142, lines 11-27). In fact, as indicated in the results of the BLASTP analysis provided herewith as Exhibit J, the

polypeptide of SEQ ID NO: 225 is 99% identical over its whole length to the human phospholipid binding protein 2 (PLPB2) but differs from PLPB2 at residue 125. As described in U.S. Patent 6,063,767, PLBP2 may be used in the diagnosis, prevention, and treatment of disorders associated with fetal development, reproduction, cell proliferation and the immune response. The specification provides numerous methods for using the claimed nucleic acids in diagnostic and therapeutic methods. These include the methods set forth in Examples 25, 26, 53, 59-61, as well as other methods described elsewhere in the specification.

Thus, the specification provides both a specific utility and a description of how to make and use the claimed nucleic acids. Accordingly, Applicants maintain that the utility requirement of 35 U.S.C. § 101 is satisfied and respectfully request that the rejections under 35 U.S.C. § 101 be withdrawn.

Rejection of Claims 1-8, 13, 14, 16, 18 and 19 under 35 U.S.C. § 112, first paragraph

Claims 1-8, 13, 14, 16, 18 and 19 were rejected under 35 U.S.C. § 112, first paragraph, on the assertion that they were not supported by either a specific and substantial or a well established utility, and thus, one skilled in the art would have not known how to use the invention. Claims 1-8, 13, 14, 16, 18 and 19 have been cancelled. However, since the utility requirement for the currently pending claims has been satisfied for the reasons stated above, Applicants respectfully submit that the requirements of the first paragraph of 35 U.S.C. § 112 have also been satisfied and respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection of Claims 1, 2, 18 and 19 under 35 U.S.C. § 102

Claim 1 was rejected under 35 U.S.C. § 102(b) because no length limitation has been placed on the complementary sequences of the claim. Claim 1 has been cancelled. However, the currently pending claims specify that the complementary sequences are fully complementary to SEQ ID NOs: 66, 76, 78 and 124 or fragments thereof. Applicants respectfully request that the rejections under 35 U.S.C. § 102 be withdrawn.

Claims 2, 18 and 19 directed to polynucleotides having at least 10 or 15 consecutive nucleotides of a selected set of SEQ ID NOs were rejected based on the assertion that they were anticipated by several references disclosing ESTs. Claims 2, 18 and 19 have been cancelled.

However, the currently pending claims recite fragments of the claimed SEQ ID NOs which are longer than the longest identical sequence in the cited references.

New Claims

New Claims 21-101 have been added. These claims are supported throughout the specification, and in particular at page 10, lines 3-8, page 44, lines 21-24, page 64, lines 14-16, page 69, lines 20-23, page 107, lines 20-22, Tables IV, V and VI, and the Sequence Listing. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 102 be withdrawn.

Conclusion

In view of the foregoing, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of the rejection is respectfully requested. Should the Examiner have any questions regarding this matter, he is invited to telephone the undersigned so that the question is resolved.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: December 22, 2000

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